Problems of Heart Rate Correction in Assessment of Drug-Induced QT Interval Prolongation

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Problems of Drug-Prolonged QTc Assessment. ***Introduction:*** **Estimation of QT interval prolongation belongs to safety assessment of every drug. Among unresolved issues, heart rate correction of the QT interval may be problematic. This article proposes a strategy for heart rate correction in drug safety studies and demonstrates the strategy using a study of ebastine, a nonsedating antihistamine.**

Methods and Results: **Four-way cross-over Phase I study investigated 32 subjects on placebo, ebastine 60 mg once a day, 100 mg once a day, and terfenadine 180 mg twice a day. Repeated ECGs were obtained before each arm and after 7 days of treatment. The changes in heart rate-corrected QTc interval were investigated using (A) 20 published heart rate correction formulas, (B) a correction formula optimized by QT/RR regression modeling in all baseline data, and (C) individual corrections optimized for each subject by drug-free QT/RR regression modeling. (A) Previously published correction formulas found QTc interval increases on terfenadine. The results with ebastine were inconsistent. For instance, Bazett's and Lecocq's correction found significant QTc increase and decrease on ebastine, respectively. The results were related ($|r| > 0.95$) to the success of each formula (independence of drug-free QTc and RR intervals). (B) The pooled drug-free QT/RR regression found an optimized correction $QTc = QT/RR^{0.314}$. QTc interval changes on placebo, ebastine 60 mg, ebastine 100 mg, and terfenadine were -1.95 ± 6.87 msec ($P = 0.18$), -3.91 ± 9.38 msec ($P = 0.053$), 0.75 ± 8.23 msec ($P = 0.66$), and 12.95 ± 14.64 msec ($P = 0.00025$), respectively. (C) Individual QT/RR regressions were significantly different between subjects and found optimized corrections $QTc = QT/RR^{\alpha}$ with $\alpha = 0.161$ to 0.417. Individualized QTc interval changes on placebo, ebastine 60 mg, ebastine 100 mg, and terfenadine were -2.76 ± 5.51 msec ($P = 0.022$), -3.15 ± 9.17 msec ($P = 0.11$), -2.61 ± 9.55 msec ($P = 0.19$), and 12.43 ± 15.25 msec ($P = 0.00057$, respectively. Drug-unrelated QTc changes up to 4.70 ± 8.92 msec reflected measurement variability.**

Conclusion: **Use of published heart rate correction formulas in the assessment of drug-induced QTc prolongation is inappropriate, especially when the drug might induce heart rate changes. Correction formulas optimized for pooled drug-free data are inferior to the formulas individualized for each subject. Measurement imprecision and natural variability can lead to mean QTc interval changes of 4 to 5 msec in the absence of drug treatment.** *(J Cardiovasc Electrophysiol, Vol. 12, pp. 411-420, April 2001)*

QTc interval, drug-induced QT interval prolongation, regression modeling, ebastine

Introduction

Assessment of drug-induced QT interval prolongation recently attracted significant attention both from drug developers and the regulatory agencies responsible for approval of new medicinal products.[1-5] Preliminary signs of proarrhythmic danger of new pharmacologic compounds can be obtained from preclinical studies.[6-9] However, the clinical importance of the preclinical signals is poorly understood, possibly due to the lack of a uniform methodology for preclinical studies. Therefore, the assessment of QT interval prolongation as a surrogate marker of potential proarrhythmia has become an integral part of Phase I and Phase II studies of drug development. The association between treatment-related QT interval prolongation and proarrhythmic cardiac toxicity of new drugs has been repeatedly reported for both cardiac and noncardiac compounds.[10-12] This association is not very direct and, with some drugs, QT interval prolongation may be completely benign. At the same time, there is no clear separation between "good" and "bad" QT interval prolongation. Therefore, any observation of QT interval prolongation during clinical studies of a new compound constitutes a signal that cannot be dismissed lightly.

Despite this importance, a standardized methodology for investigation of drug-induced QT interval prolongation does not exist. Some of the approaches used in the past clearly are inadequate because of imprecision of QT interval measurement or improper data analysis. One difficulty arises when off- and on-treatment ECGs differ in heart rate, so that some heart rate correction of the QT interval must be used. Heart rate differences may be an effect of the investigated drug or an effect of autonomic conditioning. Frequently, only very primitive approaches to heart rate correction are used despite the wide appreciation of their inappropriateness.

Dr. Malik has been a consultant to Aventis Pharma (the sponsor of the study described here) and to Almirall Prodesfarma (the owner of ebastine) and was an expert witness at the regulatory hearings when ebastine was discussed by CSM (London, United Kingdom) and the U.S. Food and Drug Administration (Washington, DC). Dr. Malik did not receive any financial support for writing this article and has no financial or other interests in Aventis Pharma and/or Almirall Prodesfarma.

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Manuscript received 12 September 2000; Accepted for publication 9 January 2001.

This article describes the methods used in evaluation of QT interval changes during a Phase I trial of ebastine, a nonsedating antihistamine.[13] Ebastine, when administered in high doses, leads to heart rate acceleration, so the evaluation of the trial required heart rate correction of the QT interval. Although some conclusions about the cardiac safety of ebastine potentially can be drawn from the results described in this article, the text is predominantly aimed at proposing a strategy for heart rate correction of QT intervals in the assessment of drug-induced QT interval prolongation.

Methods

Ebastine is a histamine H_1 receptor antagonist. It has been conceptualized as a hybrid between the potent but sedating first-generation antihistamine diphenylpyrilidine and the less potent but nonsedating second-generation antihistamine terfenadine.[13] The chief indication for treatment with ebastine is allergic rhinitis. The therapeutic dose ranges from 10 to 20 mg daily.

For the purposes of this investigation, ECG data were available from a Phase I study investigating the cardiac safety of ebastine in 32 healthy male volunteers.[14] The study was a four-period cross-over trial in which the volunteers were treated in a random order with (a) placebo; (b) 60 mg of ebastine once a day (3 to 6 times the recommended clinical daily dose); (c) 100 mg of ebastine once a day (5 to 10 times the recommended clinical daily dose); and (d) 180 mg of terfenadine twice a day (approximately 3 times the daily clinically dose recommended before withdrawal of the drug from the U.S. market). All phases were separated by sufficient washout periods. During each phase, a full panel of 12-lead ECGs was obtained in each volunteer during day −1 preceding the treatment and after 7 days of treatment when a steady state was reached. A full ECG panel consisted of recordings taken at 30 minutes before and 2, 3, 4, 5, 6, 8, and 12 hours after the projected treatment time. After 7 days of treatment, an ECG also was taken 23.5 hours after treatment.

ECGs were measured by an external clinical research organization. In each ECG, three cardiac cycles were measured using a high precision digitizing board. Mean RR interval and QT interval durations were obtained from these measurements. The data accumulated were made available for this investigation.

When administered at high doses, ebastine leads to heart rate acceleration. The on-treatment ECGs in the ebastine 100-mg arm showed a heart rate approximately 9 beats/min faster than the pretreatment or placebo ECGs. Comparisons of uncorrected QT intervals were, therefore, inappropriate for assessment of drug-induced QT interval prolongation.

Standard "Classic" Approach to Heart Rate Correction

The simplest but least defensible approach to heart rate correction is the application of a previously published heart rate correction formula. The formula by Bazett[15] has been used most frequently despite numerous reports of its inadequacy and despite the understanding that the QTc interval corrected by Bazett is artificially prolonged at heart rates >60 beats/min and shortened at heart rates <60 beats/min.[16] To compensate for the inefficiencies of Bazett's correction, it frequently has been proposed that the correction by Bazett should be accompanied by corrections by other previously published correction formulas and that results should be considered consistent if no discrepancies between the different correction approaches exist.

TABLE 1
Previously Published Heart Rate Correction Formulas Used in the Study

Author (Reference)	Parameters
Formulas of the generic form $QTc = QT/RR^{\alpha}$	
Mayeda (17)	$\alpha = 0.604$
Bazett (15)	$\alpha = 0.5$
Boudolas et al. (18)	$\alpha = 0.398$
Fridericia (19)	$\alpha = 0.333$
Yoshinaga et al. (20)	$\alpha = 0.31$
Kawataki et al. (21)	$\alpha = 0.25$
Formulas of the generic form $QTc = QT + \beta \times (1.0 - RR)$	
Sagie et al. (22) (Framingham)	$\beta = 0.154$
Ljung (23)	$\beta = 0.200$
Schlamowitz (24)	$\beta = 0.205$
Formulas of the generic form $QTc = QT + \beta/1000 \times (HR - 60)$	
Rickards et al. (25)	$\beta = 1.87$
Hodges et al. (26)	$\beta = 1.75$
Klingfield et al. (27)	$\beta = 1.32$
Wohlfart and Pahlm (28)	$\beta = 1.23$
Formula in the form $QTc = QT + \Phi(HR)$	
Karjalainen et al. (29)	Φ in a published table
Formula in the form $QTc = QT/\log_{10}(RR + \varepsilon)$	
Ashman (30)	$\varepsilon = 0.07$
Formula in the form $QTc = QT - \delta + \delta/RR$	
Kovacs (31)	$\delta = 0.12$
Formula in the form $QTc = QT - \delta/(1 + \xi \times HR) + \beta$	
Rautaharju et al. (32)	$\delta = 0.656$, $\xi = 0.01$, $\beta = 0.41$
Formula in the form $QTc = QT + \beta - \xi \times e^{(\chi \times HR)}$	
Arrowood et al. (33)	$\beta = 0.304$, $\xi = 0.492$, $\chi = -0.008$
Formulas in the generic form $QTc = QT + \beta - \xi \times e^{(\chi \times RR)}$	
Sarma et al. (34)	$\beta = -0.0149$, $\xi = 0.664$, $\chi = -2.7$
Lecocq et al. (35)	$\beta = -0.017$, $\xi = 0.676$, $\chi = -3.7$

For each formula, the table shows the original published form or its mathematical equivalent. For some formulas, more than one mathematical equivalent exists. For instance, the formula by Kovacs also may be represented by the generic form of $QTc = QT + \beta \times (HR - 60)$. The numerical coefficients correspond to both RR intervals and QT intervals measured in seconds. HR = heart rate in beats per minute; QTc = heart rate-corrected QT interval.

To demonstrate how unsatisfactory these approaches are, the data of the ebastine study were processed using 20 heart rate correction formulas selected among from the literature (Table 1). For each formula, the paired difference between the averaged pretreatment and averaged on-treatment QTc values was obtained for each subject and each arm of the study. From these differences, the QTc interval change (ΔQTc) was obtained.

The purpose of heart rate correction is to obtain QTc values that are independent of the underlying heart rate, i.e., of the RR interval. Therefore, the success of a heart rate correction formula can be expressed by calculating the correlation coefficient between the QTc values and the RR interval values in the drug-free ECGs. If this correlation

differs from zero, the correction formula used is not truly successful in correcting the QT interval for heart rate, and the reported changes in the QTc interval are influenced by the changes in the RR interval. To investigate the success of the correction formulas listed in Table 1, the correlation between the QTc interval values (according to the given formula) and RR interval values from all drug-free ECGs of the study was calculated for each formula. These correlation coefficients were taken as measures of the appropriateness of each formula.

To express how the observed QTc interval changes during the individual arms of the study depend on the success of individual correction formulas, the ΔQTc values of the individual arms of the study were plotted against correlation coefficients between QTc and RR intervals of drug-free ECGs.

Pooled Regression Analysis

In principle, every heart rate correction formula is based on the assumption that the relationship between QT and RR intervals creates a pattern that can be described mathematically. From the mathematical description of such a QT/RR pattern, a formula is derived projecting the QT interval onto a selected level of RR interval. A standard of RR interval of 1 second (i.e., heart rate 60 beats/min) is used, although this selection is based on custom rather than on any physiologic background.

Application of a previously published correction formula is based on the assumption that the mathematical relationship between the QT and RR intervals assumed by the formula is satisfied by the data at hand. Rather than relying on such an assumption, we can describe the QT/RR relationship in the analyzed data and construct a data-specific correction formula reflecting the character of the given data.

There are a number of mathematical possibilities of describing the QT/RR relationship. Both linear and nonlinear regression models have been reported. Experience obtained at our center (Malik, unpublished data) as well as by others[36] suggests that linear formulas, i.e., formulas expecting a relationship $QT = \beta + \alpha \times RR$, are potentially problematic for assessment of drug-induced QT interval prolongation. Although several different nonlinear regression models were considered in the comprehensive analysis of the cardiac safety study of ebastine, only a simple regression model of the generic form $QT = \beta \times RR^{\alpha}$ will be presented in this text. A simple mathematical consideration shows that this regression model results in a heart rate correction formula $QTc = QT/RR^{\alpha}$. To optimize such a formula for the data of this study, all the QT and RR interval data points of the baseline (day −1) recordings of all the four arms of the study were considered and their optimum regression $QT = \beta \times RR^{\alpha}$ was derived such that the correlation coefficients between the values of RR and QT/RR^{α} was zero.

In this way, the optimum heart rate correction formula $QTc = QT/RR^{\alpha}$ as derived for the drug-free data of the ebastine study and subsequently applied in the same way as any other heart rate correction formula. The optimum regression $QT = \beta \times RR^{\alpha}$ also defines a space of regression curvatures which can be used to model both the baseline and on-treatment QT/RR interval data. Such models were constructed for all four arms of the study and used for auxiliary visual judgment of QT interval prolongation under different modes of treatment.

Individual Regression Analysis

Optimizing a heart rate correction formula based on the pooled drug-free data of all participants of the study is based on the assumption that the QT/RR relationship follows the same pattern in each individual. It was reported recently that the QT/RR interval patterns have high intrasubject stability but substantial intersubject variability.[37] The application of a common heart rate correction formula to the data of each study participant may, therefore, lead to an individualized overcorrection/undercorrection even though the formula is optimized for the pooled drug-free data.

The drug-free data of each individual participating in the ebastine study were considered separately. For each subject ϑ, the individual regression formula $QT = \beta(\vartheta) \times RR^{\alpha(\vartheta)}$ was derived. Because the confidence of such an individual model depends on the number of data points available, the drug-free ECGs of each individual were taken not only from the four baseline days of each arm of the study but also from the placebo on-treatment day; altogether, 41 drug-free QT/RR interval data points were available for each individual. In this way, the drug-free variability of the QT/RR relationship was incorporated into the assessment of individual heart rate corrections.

To test whether the individual QT/RR patterns differed between different participants, *F*-tests were used to investigate for each pair of subjects ϑ_1 and ϑ_2 whether their regressions $QT = \beta(\vartheta_i) \times RR^{\alpha(\vartheta_i)}$, i = 1,2, were equal, as well as whether the exponents $\alpha(\vartheta_1)$ and $\alpha(\vartheta_2)$ were equal.

Subsequently, the individual factors $\alpha(\vartheta_i)$ were computed and an individualized heart rate correction formula $QTc = QT/RR^{\alpha(\vartheta)}$ obtained for each subject. The on- and off-treatment data in each individual were corrected using the individualized heart rate correction. The mean on-treatment QTc interval values of each study arm were compared with the averaged baseline QTc values.

Study Precision

The ability of the study to detect drug-induced QT interval prolongation depends, among others, on the precision of QT interval measurement as well as the natural variability in drug-free QTc intervals. To investigate the variability in drug-free QTc intervals, the individual subject-specific heart rate correction formulas $QTc = QT/RR^{\alpha(\vartheta)}$ were applied to the drug-free data and, for each subject, the means of the individual drug-free days were compared. Because the recordings of five different drug-free days were available in each subject, 10 comparisons of this kind were performed.

Data Presentation

Unless specified otherwise, data are presented as mean ± SD. The regression models between QT and RR intervals and the heart rate correction formulas are presented with QT and RR intervals measured in seconds. ΔQTc values are reported in milliseconds. Comparisons of QTc intervals between individual study days were based on paired comparisons of the means of QTc intervals of the individual ECG readings in each subject. A paired two-tailed *t*-test was used for this purpose. Because the multiple statistical tests

TABLE 2
Application of Previously Published Heart Rate Correction Formulas

Formula	Placebo Arm		Ebastine 60-mg Arm		Ebastine 100-mg Arm		Terfenadine Arm	
	ΔQTc	P	ΔQTc	P	ΔQTc	P	ΔQTc	P
Mayeda	4.06 ± 13.06	0.14	8.44 ± 15.67	0.015	15.73 ± 11.93	1.4×10^{-6}	20.25 ± 17.15	6.8×10^{-6}
Bazett	1.83 ± 10.46	0.40	3.76 ± 12.93	0.17	10.1 ± 9.79	4.1×10^{-5}	17.68 ± 16.05	1.8×10^{-5}
Boudolas	−0.35 ± 8.32	0.84	−0.71 ± 10.83	0.75	4.72 ± 8.59	0.013	15.19 ± 15.34	6.8×10^{-5}
Fridericia	−1.72 ± 7.28	0.26	−3.50 ± 9.92	0.097	1.38 ± 8.41	0.43	13.64 ± 15.10	0.00020
Yoshinaga	−2.21 ± 7.00	0.13	−4.50 ± 9.70	0.033	0.19 ± 8.47	0.91	13.08 ± 15.05	0.00030
Kawataki	−3.48 ± 6.53	0.016	−7.04 ± 9.40	0.0013	−2.84 ± 8.87	0.13	11.66 ± 15.02	0.00092
Sagie (Framingham)	−0.15 ± 8.11	0.93	−1.26 ± 11.11	0.58	3.32 ± 8.50	0.068	14.76 ± 15.16	8.3×10^{-5}
Ljung	2.41 ± 10.44	0.27	3.52 ± 13.51	0.21	8.80 ± 9.46	0.00014	17.42 ± 15.79	1.7×10^{-5}
Schlamowitz	2.69 ± 10.72	0.23	4.04 ± 13.81	0.16	9.39 ± 9.63	8.1×10^{-5}	17.71 ± 15.88	1.5×10^{-5}
Rickards	−2.11 ± 7.51	0.18	−2.84 ± 9.26	0.15	2.26 ± 8.32	0.20	13.35 ± 15.10	0.00025
Hodges	−2.53 ± 7.22	0.099	−3.77 ± 9.00	0.052	1.16 ± 8.26	0.45	12.87 ± 15.06	0.00035
Klingfield	−4.05 ± 6.58	0.0061	−7.09 ± 8.6	0.00051	−2.81 ± 8.57	0.12	11.14 ± 15.04	0.0014
Wohlfart	−4.37 ± 6.53	0.0033	−7.79 ± 8.62	0.00019	−3.64 ± 8.72	0.052	10.78 ± 15.07	0.0019
Karjalainen	−1.16 ± 7.64	0.46	−2.06 ± 10.25	0.34	2.88 ± 8.63	0.12	14.16 ± 15.16	0.00013
Ashman	−0.31 ± 8.30	0.85	−0.20 ± 10.45	0.93	5.31 ± 8.36	0.0049	14.93 ± 14.99	6.3×10^{-5}
Kovacs	−1.65 ± 7.86	0.31	−1.84 ± 9.60	0.35	3.46 ± 8.45	0.057	13.87 ± 15.17	0.00017
Rautaharju	−0.01 ± 8.66	0.99	0.62 ± 10.87	0.78	6.08 ± 8.48	0.0019	15.45 ± 15.28	5.3×10^{-5}
Arrowood	−0.36 ± 8.54	0.84	0.26 ± 10.58	0.91	5.76 ± 8.51	0.0030	15.17 ± 15.27	6.5×10^{-5}
Sarma	−1.58 ± 8.38	0.36	−1.08 ± 9.88	0.60	4.54 ± 8.96	0.021	14.17 ± 15.30	0.00014
Lecocq	−4.81 ± 6.94	0.0025	−7.82 ± 8.46	0.00015	−3.43 ± 9.01	0.075	10.54 ± 15.20	0.0025

For each heart rate correction formula, the table shows the differences between the averaged on-treatment and averaged baseline QTc intervals in milliseconds. The formulas correspond to the list in Table 1.

involved in the study evaluated data that were not independent between tests, the standard corrections of P values for multiple tests are not directly applicable. Thus, precise P values are shown for all comparisons.

Results

Of the initial 32 participants of the study, complete data of all four arms were available in 24 subjects. In each of these subjects, 68 ECGs were available [4 × (8+9) ECGs]. The results presented here concern these individuals.

Compared to day −1, each treatment arm led to heart rate acceleration. The averaged RR interval shortened on placebo, ebastine 60 mg, ebastine 100 mg, and terfenadine, by 58 ± 72 msec (P = 0.00065), 104 ± 83 msec ($P = 2.7 \times 10^{-6}$), 118 ± 70 msec ($P = 2.1 \times 10^{-8}$), and 54 ± 57 msec (P = 0.00014), respectively.

Previously Published Heart Rate Correction Formulas

Table 2 summarizes the results of drug-induced QT interval changes obtained with the individual heart rate correction formulas listed in Table 1. Although all formulas report QT interval prolongation on terfenadine (mean QTc prolongation 10.54 to 20.25 msec), the results of the ebastine arms are inconsistent. Some formulas report substantial and statistically significant QT interval prolongation, whereas other formulas result in QTc interval shortening on ebastine. In particular, Bazett's formula shows clear dose-related QTc interval prolongation on ebastine. Although this QTc (Bazett) prolongation does not reach the same level as the QTc prolongation on terfenadine, if taken out of context, it might be interpreted as a signal of cardiac toxicity.

Figure 1 shows the relationship between ΔQTc values reported by the different formulas and the ability of each formula to adequately correct the QT interval for heart rate as measured by the statistical independence between the QTc intervals and RR intervals in the drug-free data. The terfenadine results are almost independent of the formula used. With ebastine, on the other hand, the results are closely related to the adequacy of each formula. The highest QT interval prolongation on ebastine is reported by the formulas that overcorrect QT interval with heart rate acceleration. The lowest results (that is, QT shortening) come from the formulas that undercorrect QT interval with heart rate acceleration. In all four arms, the relationship between ΔQTc values and success (that is, noncorrelation of QTc with RR) of each formula was highly statistically significant: $r = -0.9952$, $P = 1.25 \times 10^{-19}$ for placebo; $r = -0.9503$, $P = 3.48 \times 10^{-13}$ for ebastine 60 mg; $r = -0.9618$, $P = 1.43 \times 10^{-11}$ for ebastine 100 mg; and $r = -0.9858$, $P = 2.06 \times 10^{-15}$ for terfenadine.

Pooled Regression Analysis

The pooled QT/RR interval data of baselines (day −1) of arms of the study satisfied the nonlinear regression $QT = 0.3658 \times R^{0.314}$, which corresponds to the solution $\xi = 0.314$ (95% confidence interval 0.290 to 0.338) of the correlation coefficient equation $r(RR, QT/RR^{\xi}) = 0$. Hence, the pooled baseline $QTc = QT/RR^{0.314}$ values were independent of the RR interval durations.

Figure 2 shows the regression lines for the off- and on-treatment data of the individual arms of the study corresponding to the curvatures of the heart rate correction formula $QTc = QT/RR^{0.314}$. It can be seen that although the QT interval was substantially prolonged on terfenadine, the regression lines of the off- and on-treatment on placebo, ebastine 60-mg, and ebastine 100-mg arms are within confidence intervals each of the other. At RR = 1,000 msec, the values of the off- and on-treatment regression lines on placebo, ebastine 60 mg, ebastine 100 mg, and terfenadine were 380.97 msec (95% confidence interval 377.43 to 384.51) and 380.08 msec (376.59 to 383.57); 382.69 msec (379.63 to 385.75), and 380.92 msec (376.99 to 384.85);

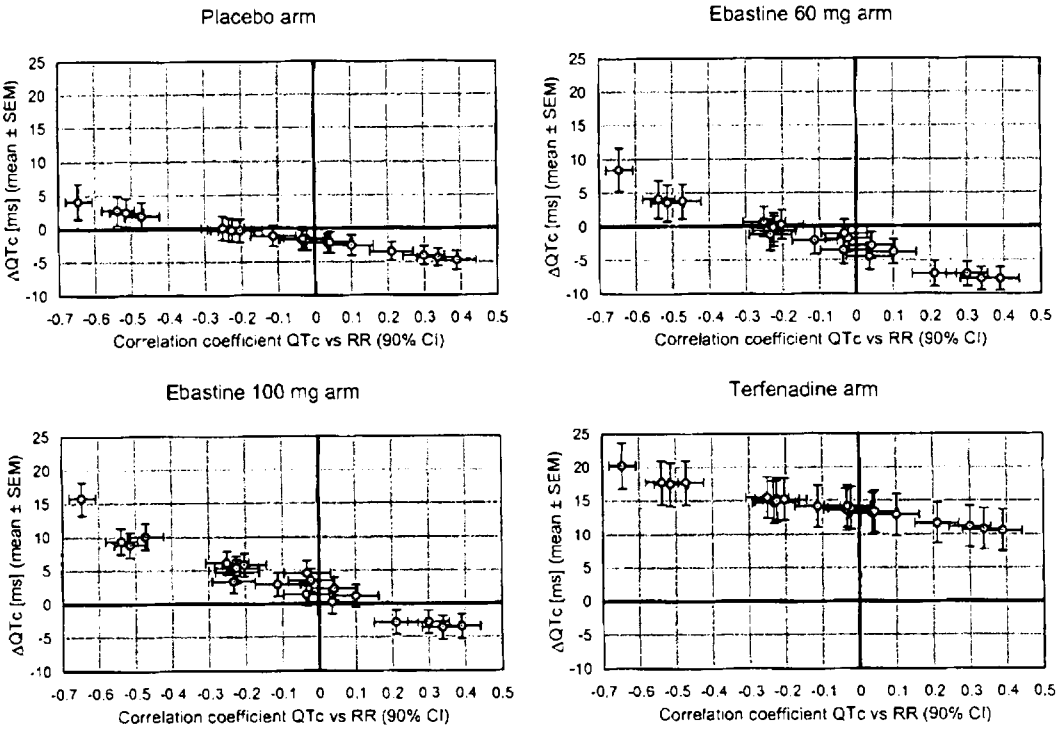

Figure 1. *For each previously published heart rate correction formula (Table 1), the panels of the individual arms of the study show the relationship between the reported QTc interval change on treatment and the heart rate correction "success" of the formula expressed by the correlation coefficient between the QTc intervals by the formula and the corresponding RR intervals in the drug-free data. Note that the results lead practically to straight lines, demonstrating that results by the different formulas are grossly determined by their correction success. Note also that the bands of the results of the placebo and ebastine arms practically pass through the points of zero QTc difference and zero correlation coefficient. CI = confidence interval; SEM = standard error of the mean.*

379.87 msec (376.41 to 383.34) and 381.39 msec (377.43 to 385.34); and 381.18 msec (377.8 to 384.55) and 396.57 msec (393.04 to 400.11), respectively. Thus, at RR = 1,000 msec, the differences between the on- and off-treatment regression lines were −0.89, −1.77, 1.52, and 15.39 msec on placebo, ebastine 60 mg, ebastine 100 mg, and terfenadine, respectively.

These results were confirmed when QTc intervals ($QTc = QT/RR^{0.314}$) in the individual arms of the study were compared. The QTc interval changes on placebo, ebastine 60 mg, ebastine 100 mg, and terfenadine were −1.95 ± 6.87 (P = 0.18), −3.91 ± 9.38 (P = 0.053), 0.75 ± 8.23 (P = 0.66), and 12.95 ± 14.64 (P = 0.00025), respectively. Although these results are very different from those observed with the Bazett correction as described in the previous section, a slight trend still exists between ebastine 60 mg and ebastine 100 mg. Although this trend is not statistically significant and is at least partly a consequence of an apparent shortening of the QTc intervals with the lower dose of ebastine relative to placebo, it might still be considered suspicious and might, under rigorous scrutiny, open discussion as to whether or not ebastine prolongs the QT interval at high doses. (The numerical differences between the shifts of regression lines and ΔQTc values exist because the regression lines consider all ECGs pooled, whereas ΔQTc values average individual ΔQTc values of separate subjects.)

Figure 3 shows the results of QTc interval changes

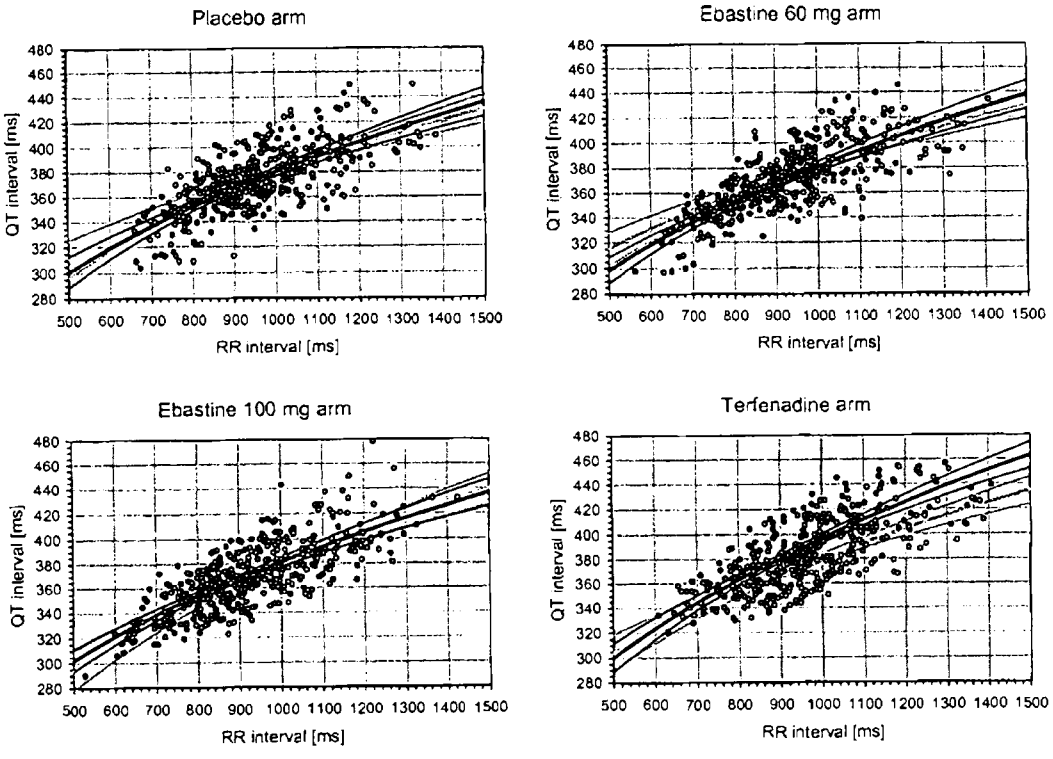

Figure 2. *Regression lines corresponding to the curvature of the pooled heart rate correction (see text for details). In each panel, the baseline (day −1) data are shown with open circles and the on-treatment data are shown with full circles. The baseline regression is shown in gray, and the on-treatment regressions are shown in black. Each regression line (bold lines) is shown with its 95% confidence bands (fine lines).*

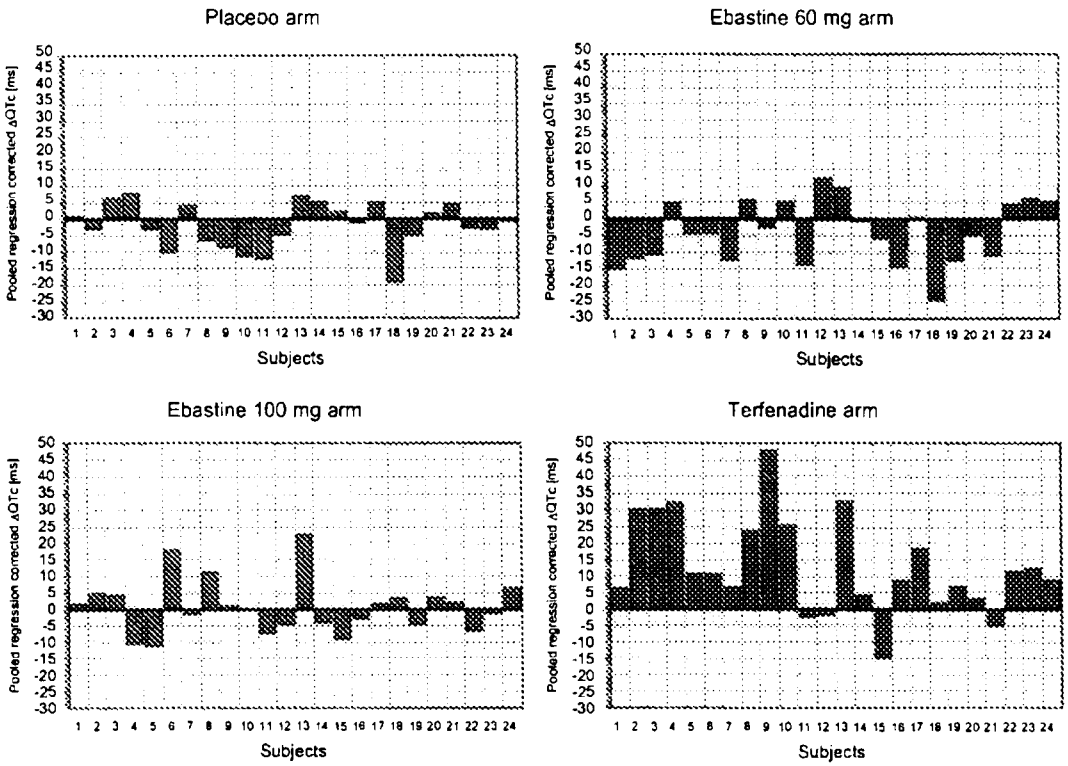

Figure 3. *Changes in QTc intervals corrected according to the pooled QT/RR data regression (see the text for details) shown for individual subjects of the study. Note the differences between the ebastine 60-mg and ebastine 100-mg arms. Despite the lack of statistical significance, the differences between these results might appear suspicious, as if a shift in the QTc interval existed from ebastine 60 mg to ebastine 100 mg.*

(QTc = QT/RR$^{0.314}$) in individual subjects. While the QTc interval prolongation on terfenadine is rather uniform across a majority of the subjects of the study, both positive and negative changes of QTc interval exists on ebastine 60 mg and 100 mg. Some of these individual changes might be interpreted as observations of subjects who are borderline susceptible to QT interval prolongation on ebastine (e.g., subject no. 13 on ebastine 100 mg, in whom the individual ΔQTc was 23 msec).

Individual Regression Analysis

The individually optimum $\alpha(\vartheta)$ values of the heart rate correction QTc = QT/RR$^{\alpha(\vartheta)}$ differed from 0.161 to 0.417 (Fig. 4). A heart rate correction that was optimum for one subject sometimes was very biased when applied to another subject. For example, α = 0.417 was the optimum correction factor for one study participant, but the correlation coefficient between the drug-free QTc and RR interval values reached −0.737 when this α value was used in another subject. For α = 0.314, the pooled optimum correction factor (see previous section), the individual correlations between drug-free QTc = QT/RR$^{0.314}$, and RR intervals ranged from −0.553 to 0.301, and their average −0.129 ± 0.219 was different from zero (P = 0.0085). Of the 24 subjects, these correlations were >0 in 6 subjects and <0 in 18 subjects.

The discrepancies between individual QT/RR interval patterns are shown in Figure 5, which shows the individual regression lines QT = $\beta(\vartheta)$ × RR$^{\alpha(\vartheta)}$. The lines also show the individual ranges of RR intervals in drug-free ECGs. These individual RR ranges were 426 ± 111 msec (range 278 to 703). The spread of the patterns of the individual

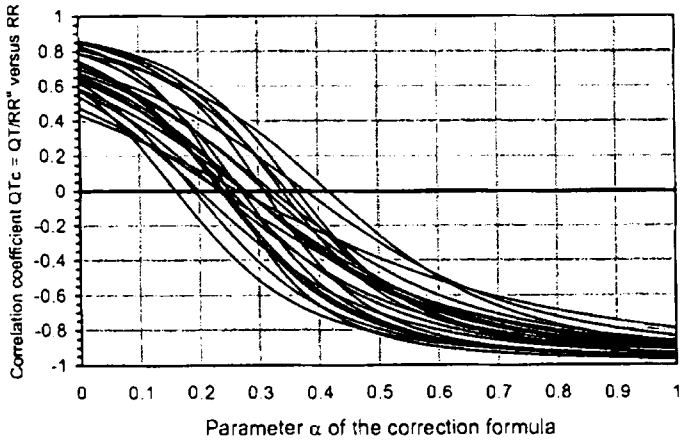

Figure 4. *For each subject of the study, the correlation coefficients between RR and QTc = QT/RR$^{\alpha}$ were calculated in all drug-free data, ranging the parameter α from 0 to 1. The individual lines in the figure show the results of individual subjects. For each subject, the individually optimum heart rate correction is found when the correlation coefficient is equal to zero (see text for details).*

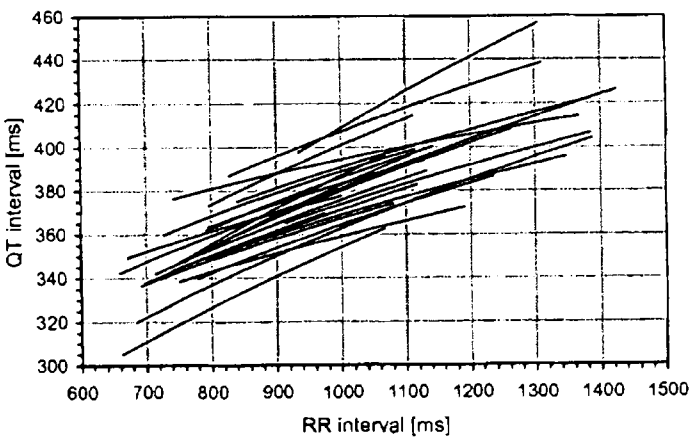

Figure 5. *Individual drug-free QT/RR regressions for individual subjects of the study. Each line corresponds to one subject and shows the optimum QT/RR nonlinear regression. The extent of each line corresponds to the range of the available drug-free RR interval data.*

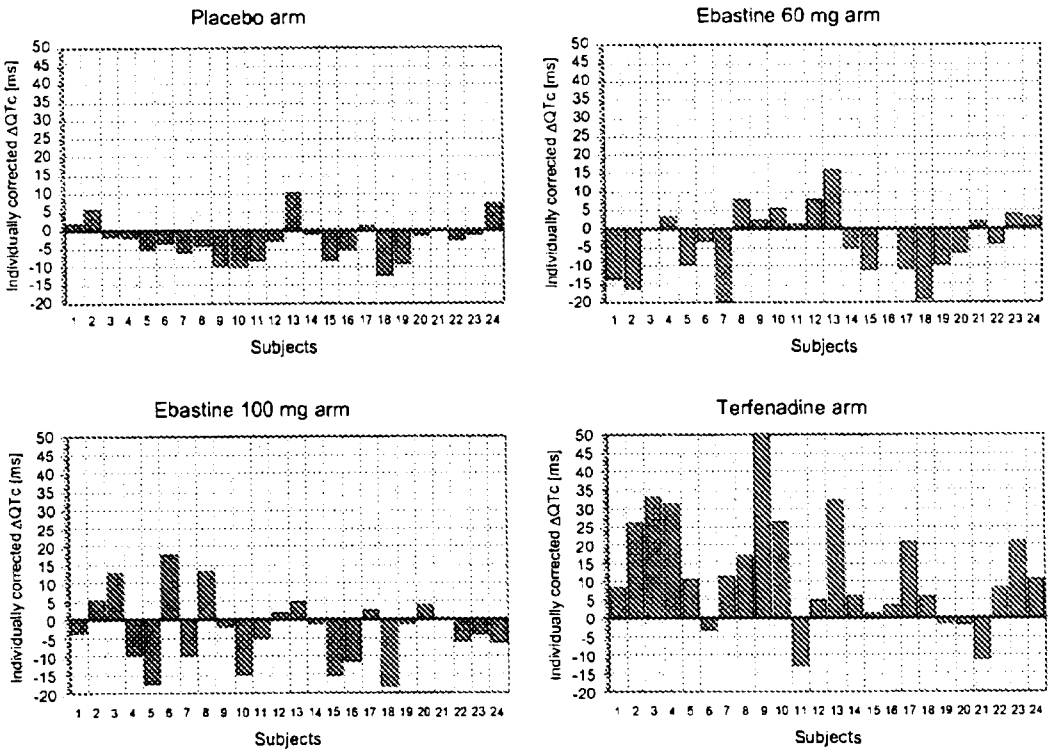

Figure 6. *Changes in QTc intervals corrected according to the individual subject-specific QT/RR data regressions (see text for details) shown for individual subjects of the study. Compare with Figure 3 and note that, in this case, no differences exist between the ebastine 60-mg and ebastine 100-mg arms.*

adaptation of QT interval to the changes in the RR interval was confirmed statistically. On average, an individual regression line of one subject of the study was significantly different from the regression lines of 17.7 ± 3.5 other subjects (range 12 to 23), and the parameter $\alpha(\vartheta)$ differed significantly from parameters $\alpha(\vartheta)$ of 3.0 ± 3.0 other subjects (range 0 to 11).

When the individual heart rate correction formulas $QTc = QT/RR^{\alpha(\vartheta)}$ were used to correct the on- and off-treatment data in individual study participants, the QTc interval change on placebo, ebastine 60 mg, ebastine 100 mg, and terfenadine were −2.76 ± 5.51 (P = 0.022), −3.15 ± 9.17 (P = 0.11), −2.61 ± 9.55 (P = 0.19), and 12.43 ± 15.25 (P = 0.00057), respectively. Figure 6 shows the results of the individual QTc interval changes in separate subjects of the study (compare with Fig. 3, e.g., subject no. 13 on ebastine 100 mg). When the individual heart rate correction models were applied, no substantial outliers appear in the ebastine arms. The results of the terfenadine arm again show systematic QT interval prolongation in the majority of the subjects.

The difference between the results obtained with the pooled and individual heart rate corrections is partly because, on the average, the individual correlation coefficient between drug-free $QTc = QT/RR^{0.314}$ and RR intervals is significantly <0. Although balanced in pooled data, the pooled heart rate correction overcorrects (i.e., leads to longer QTc intervals) more than undercorrects compared with the individually derived heart rate correction in separate subjects.

Study Precision

In the 10 separate QTc interval comparisons [based on the individual heart rate correction models $QTc = QT/RR^{\alpha(\vartheta)}$] between individual drug-free days, averaged ΔQTc values ranging from −3.03 to 4.70 msec were obtained. Because of natural variability of the QT interval, possible imprecision in ECG readings and probably pure chance, statistically significant QT interval changes were observed in 2 of the 10 comparisons: 2.67 ± 6.25 (P = 0.047) and 4.70 ± 8.92 (P = 0.017). Figure 7 shows the individual QTc interval changes related to these two comparisons. If one of these observations was made under other circumstances, the observed changes probably would be interpreted as a probable signal of drug-related QT interval prolongation, although the 30-msec threshold specified in the Committee for Proprietary Medicinal Products "Points to Consider" document was not reached in any subject.[4]

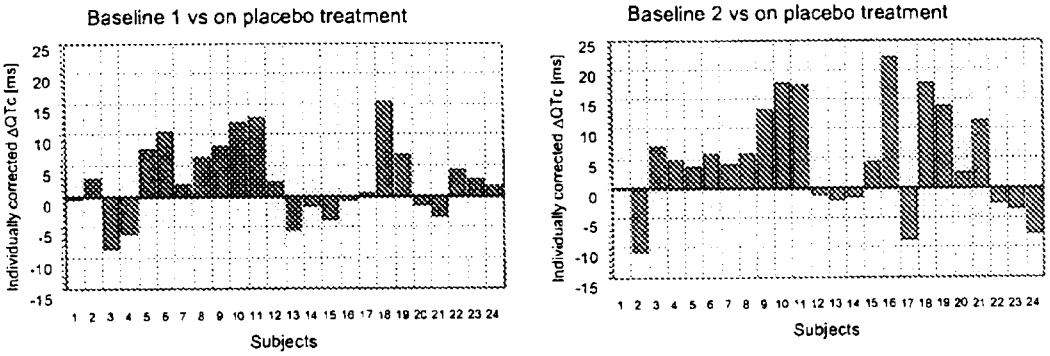

Figure 7. *Changes in QTc intervals corrected according to the individual subject-specific QT/RR data regressions (see the text for details) shown for individual subjects of the study when comparing placebo on-treatment with the data of two different baseline days.*

Discussion

Heart Rate Correction Approaches

Use of any previously published heart rate correction formula is based on the assumption that the mathematical curve corresponding to the formula provides a reasonable fit not only to the pooled drug-free data of the whole study but also to the drug-free data of each individual participant. Such an assumption must be satisfied in order to obtain QTc interval values that are truly independent of heart rate. QTc interval data need to be independent of heart rate because their comparison in off- and on-treatment recordings might otherwise be influenced by changes in heart rate, e.g., those induced by the treatment, and both false-positive and false-negative conclusions might be reached.

If any of these assumptions are not satisfied, a drug that changes heart rate (such as ebastine) might be artificially reported to change the QTc interval because of the overcorrection or undercorrection by the formula selected. As observed in the results of the analysis presented here, the finding of QTc interval prolongation or shortening in pooled data of all study participants was closely related to the adequacy of heart rate correction formula. That is, the influence of heart rate changes was not properly removed by any previously published heart rate correction formula. These various formulas should not be considered reliable, and no conclusions should be based on their application to data from studies investigating drug-related QT interval changes.

The concept of pooled regression analysis partially improves the heart rate correction by ensuring that the QTc intervals are statistically independent of the RR intervals in the pooled drug-free data of all participants of the study. Thus, the potential influence of pooled heart rate changes that invalidate the use of previously published formulas is effectively removed by the pooled regression analysis. However, the utility of the pooled regression (or of any of the published formulas) is limited by the extent to which the QT/RR relationship varies among the subjects of the study. In the data analyzed here, these intersubject variations were statistically significant.

Only the individual regression analysis is capable of ensuring that no undercorrection or overcorrection is present with any subject of the study. This type of analysis is based on the intrasubject stability of the individual QT/RR relationships.[37] The observation that individual subjects have different QT/RR relationships is in agreement with observations made independent of the data of this study.[37,38] Heart rate correction based on the mathematical models of the individual drug-free QT and RR interval data points is, therefore, superior to heart rate correction based on analysis of pooled drug-free data. Analysis of the positive control arm with terfenadine treatment clearly shows that even if the individual QT/RR relationship is considered and individual heart rate correction formulas derived, the methodology still is sensitive enough to detect moderate QT interval prolongations with a high statistical significance.

Analysis of the Ebastine Study

Picking a heart rate correction formula randomly among the battery of previously published formulas leads essentially to a random result. There is no scientific reason to prefer one particular formula (such as Bazett) and to believe that it is better than other formulas independent of the data of individual studies. For instance, the Fridericia formula ($\alpha = 0.333$) was the optimum heart rate correction for some subjects of the ebastine study, but the Bazett formula ($\alpha = 0.5$) was outside the region of the optimum heart rate correction for all of the individual subjects ($\alpha = 0.161$ to 0.417). At the same time, the Fridericia formula was near-optimum for some subjects of the study, but it led to substantial overcorrection or undercorrection in other subjects. For all these reasons, no reliable conclusion can be based on the application of previously published heart rate correction formulas in studies of drug-induced QT interval prolongation. Consequently, application of previously published heart rate correction formulas for this purpose should be considered inappropriate and potentially misleading. In particular, as shown by the superior analysis based on the individual heart rate corrections, the result obtained by applying the Bazett formula to the ebastine study was largely misleading, and the adverse signal of drug-induced QT interval prolongation was purely artificial.

Optimizing the heart rate correction formula for the pooled drug-free data was superior to the application of any previously published correction formula. At the least, the pooled regression analysis is capable of ensuring that no bias is introduced in terms of QT interval undercorrection or overcorrection in the pooled data. In this ebastine study, the result obtained with pooled regression analysis was suggestive of the absence of drug-induced QT interval prolongation, although a trend still existed between ebastine 60-mg and ebastine 100-mg arms.

The limitation of pooled regression analysis, i.e., the false assumption that all the subjects of the study have the same "physiologic" QT/RR relationship, suggests that this approach should be used only as an approximate heart rate correction when individual drug-free data are too sparse to allow the individual QT/RR relationships to be mathematically modeled. In this study of ebastine, the drug-free data were sufficient to determine the individual QT/RR relationships and the statistical differences between them. When these individual corrections were used, no QT interval prolongation on ebastine was detectable.

Possible Regulatory Implications

Regulatory agencies might have been concerned about the cardiac safety of ebastine in light of the statistically significant increase of Bazett-corrected QTc interval, which exhibited a clear dose relationship. This study shows that when proper heart rate correction is used, no QTc prolongation on high doses of ebastine is detectable, so no such concern is warranted. (The study presented here does not address a complete account of regulatory review, as it involved neither susceptible subjects nor concomitant treatment with compounds likely to affect the metabolism of ebastine. In any study of ebastine, however, proper heart rate correction would be essential.)

Precision of Detection of Drug-Induced QT Interval Prolongation

Measurement errors and genuine intersubject and intrasubject variations can lead to false-positive findings of drug-induced QT prolongation. In the ebastine study, mean

QT interval differences of almost 5 msec were noticed between different days of *drug-free* data. This does not mean that the same threshold of approximately 5 msec is applicable to other studies, because it clearly depends on the number of study participants, number of ECGs recorded on- and off-treatment, and precision of QT interval measurement. However, the observation made here suggests that similar tests should be used in all studies of drug-induced QT interval prolongation and that observations of very small QT interval increases might not necessarily constitute a true signal of cardiac toxicity.

Limitations of the Study

Assessment of the precision of ECG readings and the quality of the QT and RR interval data should be an integral part of every study investigating drug-induced QT interval prolongation. In this study, the precision of data generated by the external clinical research organization was taken for granted, even though the data were collected via a digitizing board that does not allow any feedback control. This apparatus is known to be associated with a high rate of error.[39,40] However, the intersubject variation in QT/RR patterns was so large that it is not likely to have been due to data imprecision.

Zero correlation coefficient between QTc and RR does not mean their statistical independence if the QTc/RR data are distributed along a bell- or valley-shaped curve. When constructing heart rate correction formula, the distribution of the residua of the QTc/RR regression must be studied.

The number of available data points of drug-free readings of QT and RR intervals clearly determines the confidence with which the QT/RR relationship can be mathematically modeled. Although the 41 data points available in this ebastine study seemed to be sufficient for the purposes of this investigation, no statistical assessment of the robustness of the data was performed. In future studies, the number of drug-free readings of QT and RR intervals preferably would be larger so that individual heart rate correction formulas can be constructed with substantial confidence.

To limit its size, this report described only simple regression modeling with the generic formula $QT = \beta \times RR^{\alpha}$. The complete analysis of the ebastine study involved more complex regression models,[41] the results of which were similar to those reported here. Simple regression models may not be adequate in other studies of drug-induced QT interval prolongation.

This text concentrated on the demonstration of heart rate correction principles; therefore no relationship between QTc interval changes and plasma levels of the drug are reported here. Such an investigation should be an integral part of studies investigating drug-induced QT interval prolongation.

The analysis also assumed that in each ECG, the QT is well adapted to the underlying heart rate and that the heart rate is well represented by the RR interval. This was not necessarily the case. Measuring only three consecutive RR intervals may not fully compensate for respiratory arrhythmia, making the measured RR interval not fully representative of the underlying heart rate. Because the QT interval adapts to changes in heart rate rather slowly,[42] this may lead to data imprecision. Similarly, no data were available on possible trends in heart rate during ECG recordings, which may invalidate further the correspondence between the QT and RR intervals.

There are many other factors that cause or contribute to QT interval changes and that have not been addressed in this article. These include circadian patterns, autonomic modulations, electrolyte changes, endocrinopathies, subclinical congenital long QT interval syndrome, and subclinical cardiac disease.[5,43]

Conclusion

The observations made in this report have implications for the design of studies investigating drug-induced QT interval prolongation.

Cross-over design of the studies involving both negative (placebo) and, preferably, positive control arms is crucial because it allows construction of the individual QT/RR relationship for each study participant and the conversion of the QT/RR relationship into individualized heart rate correction formulas. The number of drug-free ECGs obtained in each individual should be as large as practical in order to construct the individual QT/RR relationship with a high confidence.

Analysis based on a heart rate-correction formula derived from the pooled drug-free data should be used only in those studies (such as Phase III) in which a sufficient number of drug-free ECGs cannot be obtained from each subject. When this approach is used, its limitations should be kept in mind, and the findings should be taken only as approximate, because the bias introduced by an inappropriate heart rate correction formula may lead to both false-positive and false-negative observations.

Any of the previously published heart rate-correction formulas are, *at best*, as good as a formula derived from the pooled drug-free data of the study being analyzed, and often much worse. The use of these formulas in assessing drug-induced QT interval prolongation should be abandoned.

Acknowledgments: The author is very grateful to Drs. Robert R. Fenichel and Rashmi Shah for their kind presubmission review and their helpful comments and suggestions.

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